

Integration of Pharmacometrics and Pharmacoeconomics to Quantify the Value of Improved Forgiveness to Nonadherence: A Case Study of Novel Xanthine Oxidase Inhibitors for Gout

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MANUSCRIPT TITLE

Integration of pharmacometrics and pharmacoeconomics to quantify the value of improved forgiveness to non-adherence: A case study of novel xanthine oxidase inhibitors for gout

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CONFLICT OF INTEREST

S.M. and E.S. are, or were, employees of Pfizer. D.H-M. and D.H. have no conflicts of interest to declare.

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KEYWORDS

Pharmacometrics, pharmacoeconomics, value-based pricing, urate-lowering therapy, febuxostat, medication forgiveness

ABSTRACT

Linked pharmacometric and pharmacoeconomic models provide a structured approach for assessing the value of candidate drugs in development. The aim of this study was to assess the utility of such an approach for identifying the properties of xanthine oxidase inhibitors (XOi) providing improved forgiveness to non-adherence and estimate the maximum reimbursement price. The pharmacometric and pharmacoeconomic models were used to simulate the time course of serum uric acid concentrations, and estimate quality-adjusted life years and costs for the XOi febuxostat and a range of hypothetical analogues. Compounds with reduced clearance or increased potency were more forgiving to missed doses, however, even following relatively large changes in these properties the predicted maximum reimbursement prices represented an increase of only 19% above febuxostat 80 mg. Linked pharmacometric and pharmacoeconomic modelling methods have the potential to inform early drug development by providing an indication of pricing options that may permit reimbursement.

INTRODUCTION

Linked pharmacokinetic-pharmacodynamic-pharmacoeconomic (PKPDPE) models can provide a framework capable of testing the influence of drug pharmacology on long term clinical and economic outcomes, such as cost-effectiveness and value based pricing.¹⁻⁴ This offers distinct advantages over conventional pharmacoeconomic analyses during clinical drug development by making explicit consideration of the relation between dose taking, dose-response, health outcomes and costs. Linked PKPDPE modelling can be used to predict the likelihood of therapeutic success and quantify the implications for pricing. One application, which exploits the mechanistic properties of this approach, is in determining the influence of non-adherence on the value of treatments. This represents a natural extension to previous research in which different patterns of adherence serve as inputs to PK^{5,6} and PKPD⁷⁻⁹ models, and provides a basis for estimating cost-effectiveness in preference to cost-efficacy.¹⁰

Imperfect medication adherence can limit the benefit of treatments, result in poorer outcomes for patients, and increase healthcare costs.¹¹ Medication adherence can be decomposed into three distinct phases; 1) the initiation of treatment, 2) the degree to which a patient's dose taking matches the prescribed regimen while nominally adhering (implementation) and 3) the discontinuation of treatment (persistence).¹² The design of medicines which remain effective when dose implementation is erratic – a property known as 'forgiveness'^{13,14} – may improve treatment effectiveness under conditions of routine care and provide added value. Conventional PK and PD modelling can offer insights on the impact of variable dosing on clinical endpoints^{15,16}; however to our knowledge, there are no published methods for predicting the value of improving treatment forgiveness.

Despite the availability of effective urate-lowering therapies (ULTs) for gout, such as xanthine oxidase inhibitors (XOi) allopurinol and febuxostat, many patients fail to achieve serum uric acid target concentrations. Within clinical trials, allopurinol 300 mg/day reduced serum uric acid (sUA) concentrations to below target (6 mg/dL) in 12% – 41% of patients¹⁷⁻

²¹; and febuxostat 80mg/day in 57% – 76% of patients^{17–19}. Rates of target attainment in routine practice are also low, and range from 22% (US primary care or rheumatology clinic)²², 38% (UK primary care)²³ to 45% (UK rheumatology)²⁴. A principal cause of treatment failure is non-adherence, with as few as 40% of patients being classed as adherent (medication possession ratio > 0.8) using prescription claims data but with higher estimates obtained using other methods.^{25,26}

One potential way in which the next generation XO_i could add value is through improved forgiveness. Of the many structurally dissimilar candidate lead compounds²⁷, the potential for one to have such a property e.g. through reduced clearance or increased potency, could result in improved use-effectiveness.²⁸ More forgiving drugs that retain greater effectiveness under real world adherence would be expected to result in quality of life benefits, and potentially impact on costs, compared with existing treatments. Many jurisdictions operate a form of value-based pricing where the maximum reimbursement price is linked to the added value of a medicine, in terms of both cost and health impacts. A higher maximum reimbursement price makes it more likely that a pharmaceutical company would achieve a return on investment.

This study uses real-world adherence data and PKPDPE modelling to simulate the effectiveness and determine the value of a series of hypothetical XO_i. The aim was to assess the utility of using a PKPDPE model to link pharmacology to treatment effectiveness to the maximum reimbursement price in order to inform early decision making based on the predicted value that could be gained from developing a more forgiving drug.

RESULTS

The time courses of drug concentration in plasma and sUA concentration following single doses are presented in Figure 1 to illustrate the differences in pharmacokinetics and pharmacodynamics between febuxostat and hypothetical ULTs. The doses of hypothetical ULTs of group B (reduced IC₅₀ and dose) and C (lower clearance and dose reduction) are

reduced and consequently plasma concentrations of B4 and C4 are lower than febuxostat at 80 mg and 120 mg. A4 (reduced IC_{50}) results in the greatest reduction in sUA concentration but its effect is transient relative to C4 with an extended elimination half-life.

The predicted response rates for the hypothetical cohort over all PKPD model simulations are summarised in Table 1, where several possible measures of response have been presented. Febuxostat 80 mg and 120 mg were predicted to result in 55% and 64% of subjects with a mean sUA concentration below a 6 mg/dL target respectively. The hypothetical ULTs leading to the greatest proportion of responders was C4 (extended half-life with dose reduction) and A4 (increased potency without dose reduction) both achieving < 6 mg/dL in 75% of subjects. Scenarios assuming a greater potency and a reduced dose resulted in slightly lower response rates, down to 51%, relative to febuxostat 80 mg.

Average response rates (< 6 mg/dL) over all PKPD simulations by dose implementation groups, as shown in Table S1, are presented in Figure 2. There is very little differentiation between the ULTs when implementation is below 20% or above 90%, with the best-worst treatment differences being between 0.8 and 10.3 percentage points. Greater differentiation occurs between 20% and 90%, where the best-worst treatment difference ranges from 15.1 to 38.8 percentage points. A more pronounced pattern is observed for sustained treatment response, Figure S1, where there is no response predicted until at least 40% dose implementation. Only once implementation exceeds 70% of doses taken are high response rates (> 50%) achieved.

Table 2 presents the estimated maximum reimbursement prices at which treatments are cost effective, based on differences in estimated lifetime QALYs and costs, resulting from expected changes in flare frequency. Prices are given using either febuxostat 80 mg or 120 mg as the comparator. The highest maximum reimbursement prices are achieved by A4 and C4, which are expected to be cost effective at an annual price of £376, an increase of 19% on febuxostat 80 mg at a threshold of £20,000 per QALY.

Figure 3 shows the relationship between the responder rate and the pricing of a hypothetical ULT versus the comparator febuxostat 80 mg. The price axis is the difference between the maximum reimbursement prices at every response rate compared with the price of febuxostat 80 mg, hence the price at the response rate of 55% is fixed at £0. The two curves plot the relationship for a £20,000 per QALY cost effectiveness threshold and a probability of 10% and 50% of being cost effective at or below this threshold. This curve provides an estimate of the maximum reimbursement price for any response rate, and indicates that with 100% responder rate the maximum reimbursement price would be £140 above the annual cost of febuxostat 80 mg.

DISCUSSION

This study has demonstrated the application of linked PKPDPE models to inform drug development by estimating the maximum reimbursement price from drug pharmacology, using real-world data on medication adherence. In this case study, hypothetical XO_i with reduced dose and extended duration of action were predicted to increase the proportion of treatment responders to a similar extent as those with increased potency alone. Simulations estimated a proportion of patients responding to treatment for these more 'forgiving' ULTs of between 60% and 75% compared with 55% for febuxostat 80 mg. Based on this improvement and assuming that treatment benefit is limited to a reduction in the frequency of acute gout flares, maximum reimbursement prices were estimated of between 4% and 19% above the £317.72 current annual cost of febuxostat using a cost effectiveness threshold of £20,000 per QALY gained.

The results of this study suggest that, under conditions of imperfect adherence, reduced clearance is of equal value as a target for early candidate selection as increased potency. The identification of compounds with long elimination half-lives, while maintaining bioavailability and potency may be challenging. However, some structurally diverse and highly potent XO_i molecules have been identified and these may offer some potential lead candidates²⁷, so further research and drug discovery endeavours could be justified. While

there are alternative ULT mechanisms, such as uricosurics which lower sUA by stimulating its renal excretion, these have had limited success due to safety concerns.²⁹ Similarly, administration of the enzyme uricase (e.g. pegloticase) that converts uric acid into the more soluble component, allantoin, is not widely used due to occurrence of anti-drug antibodies, injection site reactions and its high cost.³⁰

The linkage of pharmacometrics with pharmacoeconomics remains relatively novel and there are few published examples, but has potential across a range of applications from early drug research and development²; in estimating cost effectiveness in alternative subgroups and treatment protocols³¹; in the evaluation of complex pharmaceutical interventions such as pharmacogenetic testing³²; and modelling health economics of treatments for use during pandemics³³. Pharmacometrics has been used to study issues relating to medication adherence for some time (for example Vrijens et al. 2005³⁴). This study is the first, of which we are aware, to combine adherence, pharmacometrics and pharmacoeconomics to inform early drug design decisions. In doing so this further demonstrates the value of an interdisciplinary approach and the need to interconnect existing methods to improve efficiency in drug development. As such, linked PKPDPE modelling may be seen as an additional component within the model informed drug development paradigm.³⁵

This study has advantages over conventional pharmacometric studies that do not assess the future value of compounds beyond market authorisation; and conversely, it has advantages over standard pharmacoeconomic practices which do not account for exposure response relationships. It has benefitted from a semi-mechanistic pharmacodynamic model that can account for the system dynamics resulting from intermittent dose taking. Unlike in some previous economic evaluations of ULTs^{36–38}, in this study, the clinical benefits of lowering sUA concentration have been assumed to be limited to reduced frequency of flares alone. However, this is consistent with the findings of recent meta-analyses.³⁹

Limitations of this study include the assumptions which were necessary in order to develop a model structure and to obtain parameters estimates. It has been assumed that the structure

of the pharmacometric and pharmacoeconomic models provide a sufficiently accurate representation of ULTs and their impacts to make predictions. The PKPD model was developed from a variety of published sources without fully accounting for the additional uncertainty this introduced. Aspects of the pharmacoeconomic modelling, such as the frequency of acute gout flares, relied on survey data obtained from a small number of patients. We have not considered the safety aspects of hypothetical XO_i which would inform dose selection, and would need to be accounted for in pharmacoeconomic models in terms of the cost and health implications. The adherence data was not collected in gout patients but does contain a wide variety of adherence patterns and the overall low level of adherence is consistent with studies on the routine use of ULTs.

Many jurisdictions make use of economic evaluations as a part of the decision making process of whether to reimburse medicines having obtained marketing authorisation. A new medicine failing to meet the criteria for cost effectiveness may not be marketable at a commercially viable price or gain sufficient market penetration for adequate return on investment. The framework used here provides a direct link between pharmacology and the probability of a medicine being cost-effective. These methods have the potential to inform early drug development by providing an indication of whether drug candidates possess the properties that would result in a maximum reimbursement price that justifies their progression through the long and costly drug development process.

METHODS

Overview

In the first stage, the time course of sUA was simulated based on real-world dose taking histories and using a range of drug models, representing both real-world and hypothetical XO_i. This stage was repeated a large number of times with resampling from probability distributions for patient characteristics, including baseline sUA concentration, age and weight. In the second stage the post-treatment sUA was used to predict the annual

frequency of acute gout flares over the patients' remaining lifetime and to estimate the overall costs and impacts on quality-adjusted life years.

Pharmacometric and Pharmacoeconomic Models

An existing two compartment pharmacokinetic (PK) model and multi-compartment semi-mechanistic pharmacodynamic (PD) model developed for febuxostat⁷ was used to simulate sUA concentrations. The structure of the pharmacodynamics model has been reproduced in Figure 4, while PK and PD model parameters are provided in the Supplementary Material. In addition to febuxostat at approved daily doses of 80 mg and 120 mg⁴⁰, twelve 'hypothetical' ULTs were assessed by changing the values of potency or clearance parameters for febuxostat (Table 3).

The rationale for the clearance, potency and dose adjustments is that i) reduced clearance prolongs residual drug concentration (and therefore extends the duration of action), but for an unbiased comparison a dose reduction was made to maintain the same drug exposure (area under the concentration curve); and ii) for a given concentration, a more potent drug will result in greater effect and we have, therefore, tested scenarios with and without dose adjustments. In reality, decisions concerning dose would be guided by a consideration both of the efficacy and the safety profiles of a candidate compound. We have not considered safety in this study.

The pharmacoeconomic model used a Markov state-transition structure with a 3-month time cycle to estimate costs and QALYs in a cohort of patients eligible for ULT. An overview of the model structure is given in Figure S2, model parameters are provided in the Supplementary Material and a comprehensive description of the model can be found elsewhere.¹ The approach to modelling cost effectiveness is consistent with the methods of the National Institute for Health and Care Excellence in the UK⁴¹, adopting the cost perspective of the National Health Service in the UK, a lifetime (50 year) time horizon, and

costs and QALYs both discounted at a rate of 3.5% per annum.⁴² The model was implemented in R version 3.5.1.⁴³

For each ULT in Table 3, a nominal 10,000 patients are initially allocated to treatment and distributed between four sUA sub-states (<6, 6 to <8, 8 to <10 and ≥ 10 mg/dL) based on the results of PKPD simulations. In each model cycle, a proportion of patients discontinue treatment and are redistributed between the sUA sub-states to an untreated sUA distribution. A proportion also move to a dead state according to all-cause mortality probabilities derived from life tables for England and Wales in 2015.⁴⁴ The model conservatively assumes that the only benefit of reducing sUA concentrations is to reduce the frequency of acute gout flares. A flare frequency distribution was derived from cross-sectional survey data⁴⁵ across five categories; 0, 1-2, 3, 4-5 and 6+ flares per annum. Fewer gout flares then result in improved quality of life and reduced treatment costs.⁴⁵

Adherence Data

Adherence to ULTs was assumed from real world data on chronic treatment (119 subjects, 15,959 individual doses and follow-up between 90 and 529 days^{46,47}) using electronically-recorded pill bottle cap opening times⁴⁸ (MEMS, Aardex Group). Many of the adherence patterns are characterised by an implementation phase of varying levels of adherence followed by a complete cessation of doses prior to the end of the observation period. Instances of non-adherence following the implementation phase were discarded, as discontinuation was modelled separately in the pharmacoeconomic model. The distribution of dose implementation is given in Table S1, while figures showing all doses taken by every subject are provided in Figures S3-S7 in the Supplementary Material.

Simulation Modelling

Linked PKPDPE simulations were performed for each of the 14 ULTs. The pharmacometric stage was performed for each of the 119 real world adherence patterns ranging from 57 days to 529 days of dose implementation. Each simulation was repeated 500 times with

resampling from individual random effects and from the probability distributions (based on clinical trial baseline data¹⁹) assumed for subject covariates including age (log-normal), weight (log-normal) and baseline sUA concentration (normal). However, uncertainty in the parameter estimates, in the estimates of the random effects parameters and residual variability was not included in PKPD simulations.

The simulated sUA time courses were used to generate post-treatment sUA concentration distributions across four states for use in the pharmacoeconomic model. These were obtained by taking the mean of the simulated daily sUA levels for days beyond day 50 but before discontinuation. The primary measure of treatment response for a ULT, equivalent to the primary outcome measure used in many clinical trials^{17–19}, is the proportion of subject simulations in the < 6 mg/dL state. Further alternative measures of treatment response were derived using daily sUA concentrations for all available days beyond day 50 but before discontinuation. The proportions of subject simulations which were < 6 mg/dL for at least 80, 70, or 60% of days have been calculated to measure sustained response. Although not reported in clinical trials, there are more likely to be associated with a reduction in gout symptoms⁴⁹.

In each iteration of the pharmacoeconomic model, the process of collapsing sUA concentration measurements on to the four sUA states was repeated with random sampling to bootstrap and propagate PKPD variability. Other pharmacoeconomic model inputs, such as flare frequency distributions, health state utilities and discontinuation rates, were also varied according to probability distributions used to represent uncertainty regarding their true value. Further details of the model parameters and probability distributions are summarised in the Supplementary Material. A total of 5,000 pharmacoeconomic models were performed for each unique ULT and adherence pattern combination.

The outputs of the pharmacoeconomic model for each ULT are the mean per patient lifetime QALYs and costs associated with gout following the initiation of treatment and the mean number of cycles of drug supplied. All hypothetical ULTs were compared with febuxostat 80

mg or 120 mg, both with an annual price of £317.72.⁴⁰ Cost effectiveness thresholds were used to determine whether a higher cost treatment is sufficiently effective to justify reimbursement. We have used a cost effectiveness threshold of £20,000 per QALY gained which is routinely used in the UK.⁵⁰

Where a hypothetical ULT is more effective than febuxostat 80 mg we have estimated the maximum price at which the hypothetical ULT would be cost effective using the mean QALY and cost differences. The maximum cost effective price can be found by solving equation 1 for P_h when net monetary benefit (NMB) is equal to zero.

$$NMB = \lambda \Delta Q - \left(\Delta C_{ND} + (S_h * P_h - S_f * P_f) \right) \quad (1)$$

NMB is the net monetary benefit, λ is the cost effectiveness threshold, ΔQ is the difference in lifetime QALYs, ΔC_{ND} is the difference in non-drug costs, S_f is the number of cycles febuxostat 80/120 mg, P_f is the price of febuxostat 80/120 mg, S_h is the number of cycles of hypothetical ULT, and P_h is the price of the hypothetical ULT.

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AUTHOR CONTRIBUTIONS

D.H.-M., E.S., S.M., and D.A.H. wrote the manuscript; D.H.-M. and D.A.H. designed the research; D.H.-M. performed the research; D.H.-M. analyzed the data.

STUDY HIGHLIGHTS

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Linked pharmacometric and pharmacoeconomic modelling has been shown to have potential utility across a range of different applications.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study has sought to extend linked pharmacometric and pharmacoeconomic models to account for realistic drug adherence and quantify the value of drugs with improved forgiveness to missed doses.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This was a case study of the application of linked pharmacometric and pharmacoeconomic models to quantify the value of hypothetical xanthine oxidase inhibitors for treating gout, based on their pharmacology. The maximum reimbursement price for hypothetical agents with increased potency or reduced clearance was estimated based on treatment success rates. This novel framework provides a direct link between drug pharmacology and the probability of a drug being cost-effective while explicitly accounting for realistic medication adherence.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS?

These methods have the potential to inform early drug development by providing an indication of whether drug candidates possess the properties that would result in a maximum reimbursement price that justifies their progression through the long and costly drug development process.

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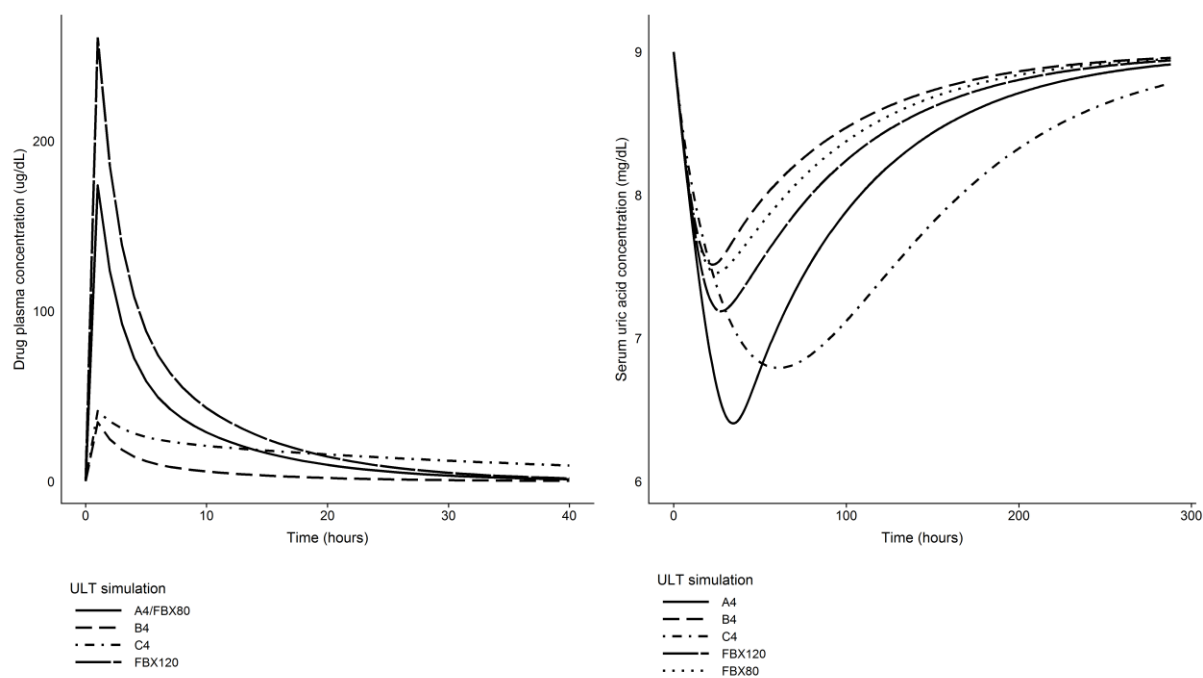


Figure 1. Simulated drug plasma concentration and serum uric acid time course following a single oral dose (taken at hour 12) of febuxostat 80mg or 120mg as well as 3 hypothetical ULTs (simulations used a reference subject of age 60, weight 100 kg, and baseline sUA of 9 mg/dL)

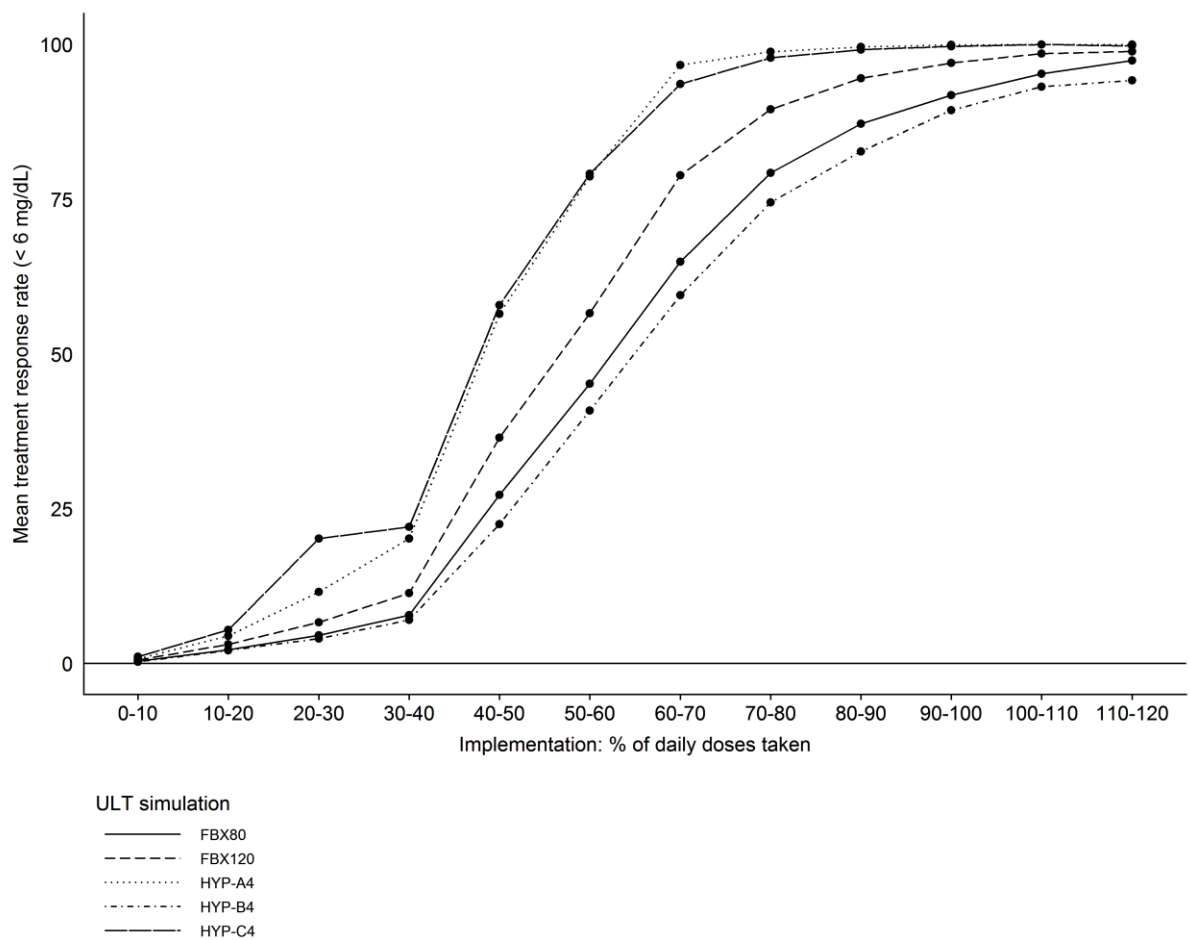


Figure 2. Mean treatment response rates for hypothetical ULTs compared with febuxostat 80mg by dose implementation using response defined using mean daily sUA concentration below 6 mg/dL target

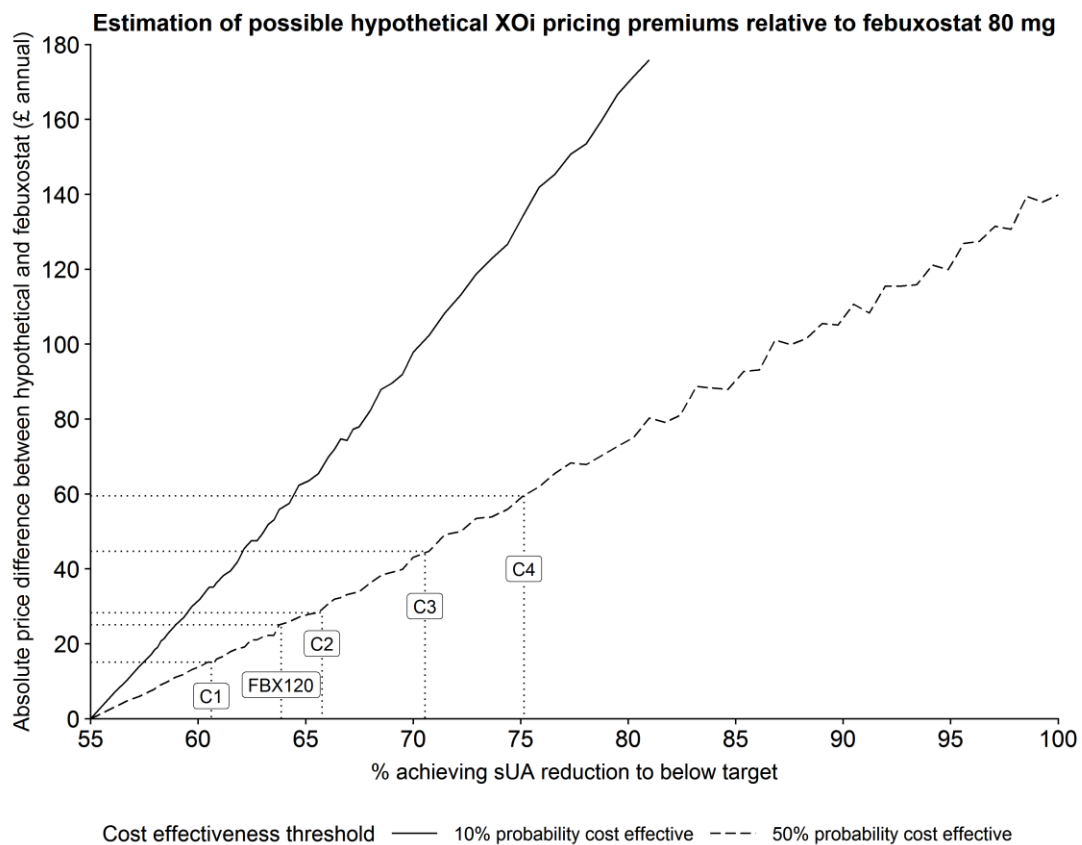


Figure 3. Curve of estimated pricing to achieve cost effectiveness versus febuxostat 80 mg with probability of 50% and 10% at a willingness to pay threshold of £20,000

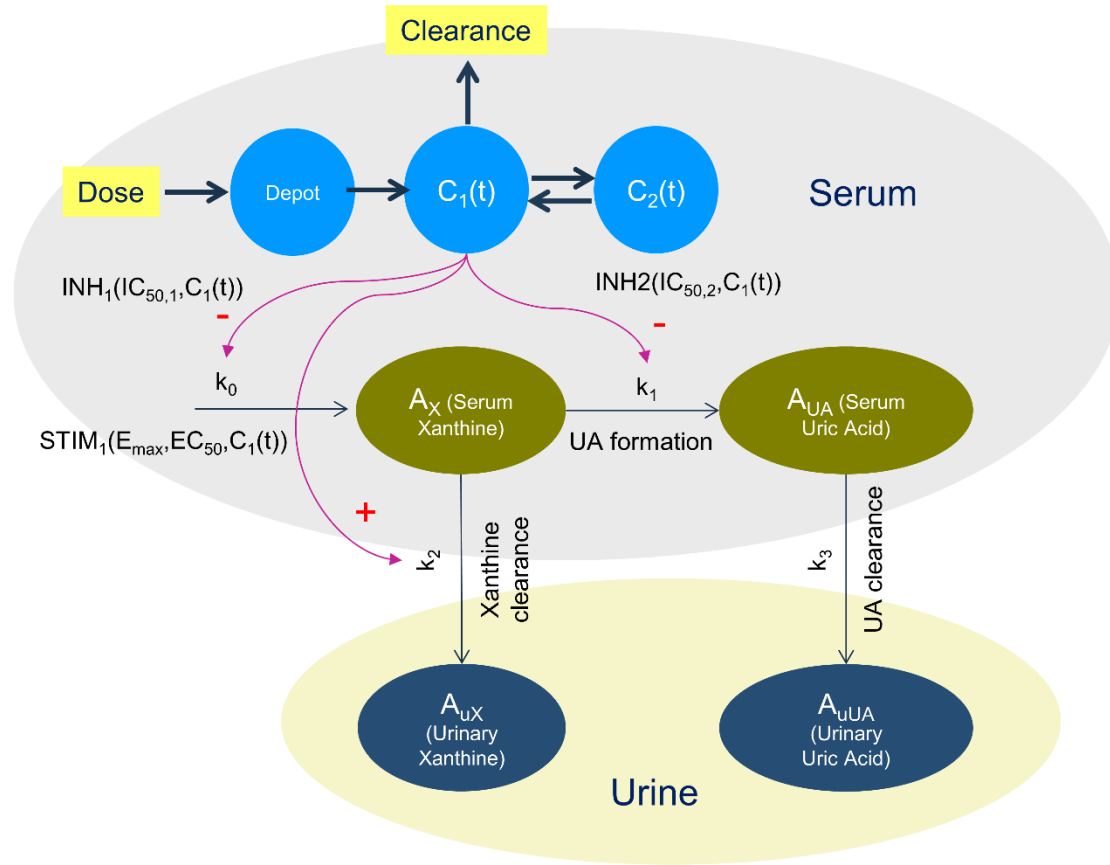


Figure 4. Diagrammatic and mathematical representations of the pharmacodynamics of dual-urate lowering therapies. k_0 , k_1 , k_2 and k_3 are the rate parameters for the production of xanthine, xanthine to uric acid conversion, removal of xanthine to urine and removal of uric acid to urine, respectively. INH_1 , INH_2 , and $STIM_1$ are the pharmacodynamic model drug functions. A_X and A_{UA} are the total time-varying amounts of xanthine and uric acid in serum, respectively. A_{uX} and A_{uUA} are total amounts of xanthine and uric acid removed to urine, respectively. $C_1(t)$ and $C_2(t)$ are the plasma concentrations of drug in the central and peripheral pharmacokinetic compartments respectively.